The Transition From Hypertrophy to Failure
How Certain Are We?

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Hypertensive heart disease is a major contributor to cardiovascular morbidity and mortality, especially in African Americans, in whom LV hypertrophy is 2 to 3-fold more common in the general population as compared with whites.1 In the classic paradigm of hypertensive heart disease, concentric hypertrophy (a nondilated, thick-walled left ventricle typically with a normal left ventricular ejection fraction [LVEF]) is a common precursor to LV failure (an increased LV volume with reduced LVEF).2 Although molecular triggers of this transition from concentric hypertrophy to failure have been the subject of intense investigation, there are no previous large, longitudinal cohort studies in humans demonstrating that this progression occurs frequently. The transition from concentric LV hypertrophy to failure has been well demonstrated in animal models including the spontaneously hypertensive rat,3 or after aortic banding4 or transgenic manipulation,5 and also in humans with aortic stenosis6 or familial hypertrophic cardiomyopathy.7 Whether this paradigm faithfully represents the natural history of hypertensive heart disease is not yet known (Figure). An alternative paradigm is that the LV response to elevated blood pressure is either hypertrophy or failure, with transition between the 2 uncommon in the absence of an interval cardiac injury.

There appear to be considerable data supporting the classical paradigm of the progression of hypertensive heart disease. Hypertension is a major risk factor for LV hypertrophy8 and in the development of clinical heart failure.9 In large clinical trials of patients with heart failure and reduced LVEF, the most common cause of the reduced LVEF in African Americans is hypertension.10 Patients with hypertension-related concentric LV hypertrophy, despite a normal LVEF, have reduced systolic function as assessed by LV midwall fractional shortening.11,12 Nevertheless, major limitations remain in these data as they pertain to assessing the accuracy of the paradigm of hypertensive heart disease. First, the proportion of the heart failure attributed to hypertension that is associated with a preserved or reduced LVEF is not known. Given that concentric LV hypertrophy is associated with heart failure in the setting of a preserved LVEF,13 data demonstrating that concentric LV hypertrophy is a major risk factor for heart failure with a reduced LVEF are needed. Second, in clinical trials of patients with heart failure caused by a reduced LVEF, it is not known whether those patients with hypertensive cardiomyopathy had antecedent concentric LV hypertrophy. Third, although reduced midwall fractional shortening is associated with adverse outcomes in hypertensives,14 whether it predicates the development of overt LV failure is not known.

It is also critical to distinguish whether there is superimposed coronary artery disease and myocardial infarction when evaluating the transition from concentric LV hypertrophy to failure. In early case series, it was noted that hypertensive patients whose death was attributed to heart failure often had concomitant severe coronary artery disease.15 LV hypertrophy subsequently was shown to be a risk factor for incident coronary heart disease including myocardial infarction.16 If a patient sustains sufficient myocardial necrosis from infarction, whether or not he or she has concentric LV hypertrophy, then a reduced LVEF will develop. How often patients with concentric LV hypertrophy develop LV failure in the absence of an interval myocardial infarction remains unknown.

Additional insights into the transition from concentric LV hypertrophy to failure are gained from 2 recently completed studies of subjects who underwent serial echocardiography and longitudinal follow-up.17-18 The first was a retrospective analysis of the Parkland Memorial Hospital echocardiography database, which demonstrated that of 159 predominantly middle-aged African American hypertensives with concentric LV hypertrophy and a normal LVEF, only 18% developed a reduced LVEF after a follow-up of ~4 years.18 Furthermore, nearly half of those who did develop a low LVEF had an interval myocardial infarction. The second analysis was from the Cardiovascular Health Study.17 In the older adult white subjects included in this analysis, increased baseline LV mass was a risk factor for the development of a reduced LVEF after 5 years of follow-up, independent of coronary artery disease or myocardial infarction; however, the majority of cases of LV hypertrophy were of an eccentric pattern (ie, increased LV mass caused by a dilated left ventricle with normal relative wall thickness). In a multivariable analysis, concentric LV hypertrophy was not an independent risk factor for the development of a low LVEF, possibly because of the small number of subjects (n=26) who had concentric LV hypertrophy in this study. To my knowledge, there are no other longitudinal studies that address how often concentric LV hypertrophy progresses to LV failure.
Potential pathways in progression of hypertensive heart disease. Hypertension can lead to concentric left ventricular hypertrophy (LVH), characterized by nondilated, thick-walled left ventricle (arrow, top left). After “transition to failure,” the LV is dilated with reduced LVEF. Coronary artery disease often via MI is a common contributor to this transition (first horizontal arrow). Whether concentric LVH commonly leads to low EF in absence of an interval MI or significant coronary artery disease is uncertain (second horizontal arrow). If LVH is not common precursor to LV failure in absence of MI, then one would have to postulate that hypertension can lead directly to LV failure without MI (arrow, top right) to explain the observation that hypertension, in absence of MI, is attributed as most common cause of cardiomyopathy in African Americans in clinical trials of heart failure with reduced LVEF.10 Symptomatic heart failure can occur either with LVH and normal EF or with LV failure and reduced EF (vertical arrows, bottom).

In this issue of Circulation, the Multi-Ethnic Study of Atherosclerosis (MESA) investigators have provided additional insights about the transition from LV hypertrophy to failure.19 Using state-of-the-art cardiac MRI including myocardial tagging in 441 subjects free of known cardiovascular disease, Rosen et al demonstrated that systolic function, as measured by peak systolic circumferential strain or LVEF, decreased with higher LV mass/volume ratio in men. In women, circumferential strain was also lower in those with reduced LVEF. Circumferential strain was also lower in those with increased blood pressure. However, when considering men and women in unadjusted analyses, there was no such association with LVEF. When stratified by coronary artery distribution, the inverse association of regional strain and the LV mass/volume ratio was the most robust in the territory of the left anterior descending artery when considering men and women in unadjusted analyses, although this pattern appeared not to be consistent in women in multivariable analysis. Nevertheless, these data suggest that there may be heretofore unappreciated regional differences in LV systolic function in response to concentric remodeling.

It is tempting to speculate that individuals in the highest quintile of LV mass/volume ratio with reduced circumferential strain have been imaged during the “transition to failure”; in other words, they are on the path to LV failure characterized by LV dilation and an overtly reduced LVEF. There are important caveats to this interpretation, however. First, the data from Rosen et al are cross-sectional, making it difficult to assign causality. For example, an alternative hypothesis is that the impaired systolic function, as measured by reduced circumferential strain, led to LV hypertrophy and an increased LV mass/volume ratio, rather than resulting from it. Second, the LV volumes were decreased in the highest quintile of LV mass/volume ratio, whereas LV volume is increased with LV failure. Third, there was no significant association of other measures of concentric remodeling such as posterior and septal LV wall thickness with regional circumferential strain.

To resolve these unanswered questions, serial imaging studies are needed to clarify the progression of hypertensive heart disease, in a fashion analogous to that done in patients with ischemic heart disease after myocardial infarction, although such studies for hypertension likely will need to be completed over a longer (5 to 10 years) time frame. Only then will we know whether concentric LV hypertrophy is a common precursor to LV failure. If the present paradigm is proven inaccurate by such longitudinal studies and the common pathway to LV failure in the absence of myocardial infarction occurs without antecedent LV hypertrophy, then we will have substantially refined our phenotypic characterization of patients with hypertension. Such an advance would be an important step toward identifying those risk factors, including genetic variation, that predispose individuals to develop either LV failure or LV hypertrophy in response to increased blood pressure.

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References


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